

Complete asymmetric amplification of ethylenediammonium sulfate using an abrasion/grinding technique†

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Complete asymmetric amplification of ethylenediammonium sulfate was achieved under continuous dissolution/crystallization conditions using an abrasion/grinding method.

Chiral preference for L-amino acids, D-sugars and in other essential biomolecules is a characteristic of living systems. The origin of biological homochirality is one of the outstanding mysteries facing scientists today.^{1,2} Different theories have been brought forward to address the original imbalance between molecules of opposite chirality, including the parity violation energy difference (PVED),³ the influence of circularly polarized light (CPL),⁴ selective adsorption on chiral mineral surfaces,⁵ and statistical fluctuations.⁶ Furthermore, this initial imbalance must be amplified in order to reach homochirality (*i.e.* complete asymmetric amplification).⁷

Although achiral molecules normally crystallize into achiral crystals, in some cases they can form enantiomorphous crystals.^{8,9} The chiral crystallization of sodium chlorate has been known for over 100 years.¹⁰ It was shown by Kipping and Pope that when crystallized from an aqueous solution a statistically equal number of *dextrorotatory* and *levorotatory* sodium chlorate crystals was obtained (*i.e.* a conglomerate), and a state of chiral symmetry is reached. Our research group has been investigating the crystallization of ethylenediammonium sulfate, $(\text{H}_2\text{NCH}_2\text{CH}_2\text{NH}_2)\cdot\text{H}_2\text{SO}_4$, another achiral molecule that forms chiral crystals.¹¹ As expected, the slow crystallization of ethylenediammonium sulfate from an aqueous solution gives a statistically equal number of *dextrorotatory* and *levorotatory* crystals.

Chiral symmetry breaking is a process which spontaneously generates an unequal mixture of enantiomers from a racemic or achiral state.^{12,13} Chiral symmetry breaking of sodium chlorate was reported by Kondepudi *et al.* where it was shown that if an aqueous solution of sodium chlorate was stirred during crystallization, almost all of the crystals in a particular sample had the same chirality.¹⁴ It was proposed that this total spontaneous resolution is a consequence of crystal growth

exclusively occurring on the surface of existing crystals of the same chirality (*i.e.* secondary nucleation) and suppression of crystal nucleation of the opposite chirality.^{14,15} More recently, Viedma reported the symmetry breaking and asymmetric amplification of racemic sodium chlorate and sodium bromate crystals under abrasion/grinding conditions where continuous dissolution and secondary crystallization cycles lead to complete asymmetric amplification.^{16,17} Viedma also showed that only a slight initial imbalance (5% crystal enantiomeric excess) was required to direct the asymmetric amplification process in a particular direction. This chiral amplification process is thought to be the result of autocatalytic secondary nucleation working in conjunction with Ostwald ripening.¹⁸ It is a non-equilibrium process where the dissolution of the solid phase is thermodynamically driven and the growth (and amplification) of the more abundant crystals is under kinetic control.^{19–21}

A crystallographic description of ethylenediammonium sulfate was first reported by Groth in 1910.²² Ethylenediammonium sulfate crystallizes in the tetragonal chiral space group, $P4_1$, where the ethylenediammonium cation adopts a chiral *gauche* conformation resulting in an overall helical arrangement of the $[\text{H}_3\text{NCH}_2\text{CH}_2\text{NH}_3]^{2+}$ and $[\text{SO}_4]^{2-}$ ions in the unit cell (Fig. 1).²³

Herein, we report the complete asymmetric amplification of ethylenediammonium sulfate using an abrasion/grinding method. Apart from the experiments on sodium chlorate and sodium bromate reported by Viedma, to our knowledge this is the only other example to date of asymmetric amplification by thermodynamic/kinetic feedback near equilibrium.²¹ Ethylenediammonium sulfate was synthesized by the dropwise addition of sulfuric acid to ice-cooled ethanolic ethylenediamine (ESI†). The asymmetric amplification process was carried out by stirring solid ethylenediammonium sulfate in a

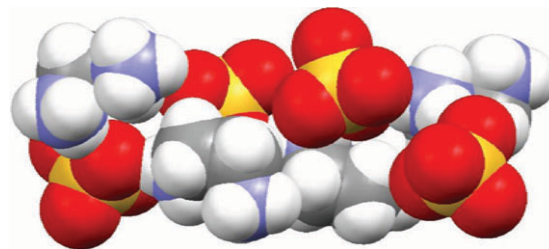


Fig. 1 Three-dimensional crystal structure of ethylenediammonium sulfate. The ethylenediammonium cation adopts a chiral *gauche* conformation enforced by hydrogen bonding with sulfate anions.²³

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† Electronic supplementary information (ESI) available: Synthesis of ethylenediammonium sulfate (EDS), preparation of EDS saturated solution, closed system setup for the abrasion/grinding experiments, crystal seeding technique, and determination of EDS crystal chirality using a polarized light microscope. See DOI: 10.1039/b716977a

saturated solution in the presence of grinding media in a closed system (ESI†). Throughout the amplification process, small aliquots of crystallites were sampled and allowed to grow larger in a saturated solution overnight (ESI†). Approximately 150 crystals (*ca.* 1.6 mm × 1.6 mm × 0.3 mm) were collected from each seeding experiment, their chirality was determined using a polarizing microscope (ESI†) and the crystal enantiomeric excess (CEE) at each sampling time was calculated as: $CEE = |(N_d - N_l)/(N_d + N_l)| \times 100$; where N_d represents the number of *dextrorotatory* crystals and N_l represents the number of *levorotatory* crystals. Abrasion/grinding of ethylenediammonium sulfate was carried out at different stirring rates using either 3 mm glass beads or 0.8 mm ceramic beads as grinding media. The duration of stirring required to reach chiral purity under different experimental conditions shows that homochirality is attained in less time at higher stirring rates. The time required to obtain complete asymmetric amplification using 3 mm glass beads as grinding media was *ca.* 20 days and *ca.* 7 days with stirring rates of 480 rpm and 1100 rpm, respectively. Clearly there is a significant decrease in time to achieve complete asymmetric amplification as the stirring rate is increased. It is interesting to note that the rate of asymmetric amplification of ethylenediammonium sulfate is much slower than that of sodium chlorate where chiral purity is achieved after *ca.* 1 day at 600 rpm with 3 mm glass beads. In order to increase the rate of asymmetric amplification further, smaller diameter grinding media was used. With stirring rates of 2400 rpm and 4800 rpm using 0.8 mm ceramic beads as grinding media, homochirality was achieved after *ca.* 3 days and *ca.* 1.5 days, respectively. When the kinetics of the process was monitored, an asymptotic trend was observed during the nonlinear autocatalytic process (Fig. 2). Complete asymmetric amplification was also achieved after *ca.* 6 days using a rotary shaker operating at *ca.* 40 Hz with 0.8 mm diameter ceramic beads as grinding media.

The results for eight separate experiments demonstrate a handedness preference towards *levorotatory* crystals. This is due to the fact that the chirality of the starting material prepared in our lab has a 4.5% CEE of *levorotatory* crystals as determined by the seeded growth of 2177 crystals. We were unable to synthesize a true racemic mixture‡ of ethylenediammonium sulfate starting from ethylenediamine and sulfuric acid.²⁴ This may be due to the presence of trace chiral impurities (cryptochiral environment) in our laboratory as was also described for the directed asymmetric amplification observed by Viedma for sodium chlorate and sodium bromate.²⁵ We propose that a cryptochiral environment during the synthesis of ethylenediammonium sulfate causes an initial chiral imbalance in our starting material. Asymmetric amplification towards both *dextrorotatory* and *levorotatory* crystals was observed when an equal mixture of ground *dextrorotatory* and *levorotatory* ethylenediammonium sulfate crystals was used as the starting material for the grinding/abrasion experiment. Furthermore, when the initial mixture was purposely biased with an excess of one chiral form of the crystals (20% CEE), the asymmetric amplification of the ethylenediammonium sulfate crystals was directed towards the original bias as expected. The mechanism of asymmetric amplification of ethylenediammonium sulfate is thought to involve the same

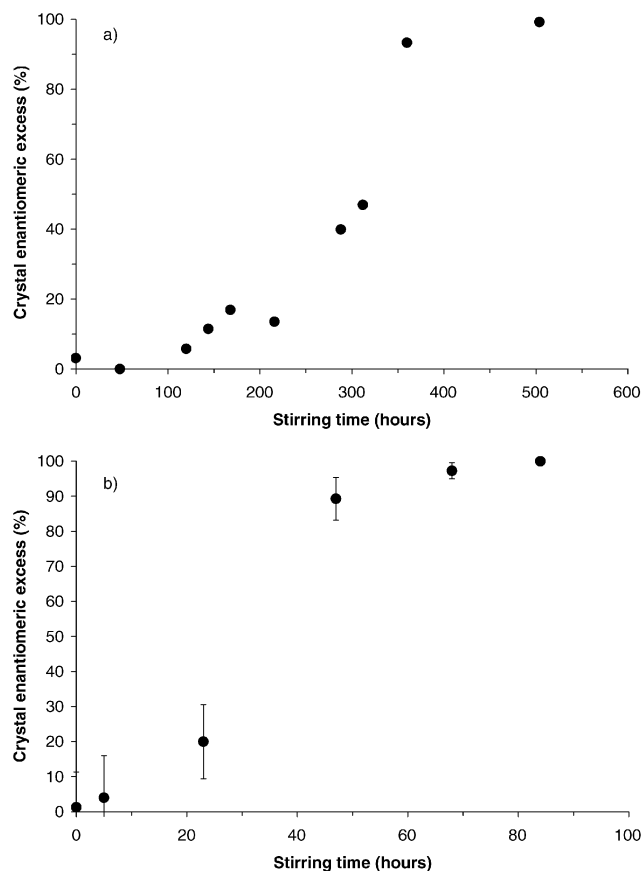


Fig. 2 Asymmetric amplification of ethylenediammonium sulfate by abrasion/grinding. (a) Evolution of crystal enantiomeric excess with time using 3 mm glass beads as grinding media with a stirring rate of 480 rpm. (b) Evolution of crystal enantiomeric excess with time using 0.8 mm ceramic beads as grinding media with a stirring rate of 2400 rpm.

steps as described by Viedma for the asymmetric amplification of sodium chlorate. First, the ethylenediammonium sulfate crystals in saturated solution experience continuous dissolution/crystallization under abrasion/grinding in the closed system where small fragments are broken off from the initial crystals during the grinding process. According to the Gibbs-Thompson equation, small crystallites have a higher solubility than larger ones and therefore dissolve more readily into achiral molecules which can subsequently add to existing crystals. This recycling process is critical since any enantiomeric imbalance will be amplified at the expense of the handedness in minority in a nonlinear manner *via* Ostwald ripening.²¹ Concisely, the direction of symmetry breaking of a racemic system depends on chance during the abrasion/grinding process and the associated recycling process amplifies this initial broken symmetry towards homochirality.

In summary, complete asymmetric amplification of ethylenediammonium sulfate was achieved using a previously reported abrasion/grinding method. We have shown that the time to achieve complete asymmetric amplification is dependent on the efficiency of the grinding process (*i.e.* increasing the stirring rate or decreasing the size of the grinding media both result in a faster rate of asymmetric amplification).

Further studies will be required to obtain a detailed relationship between the grinding efficiency and the time dependence for reaching chiral purity. The preference of our system towards the amplification of *levorotatory* crystals was due to the slight excess of *levorotatory* crystals in our starting material (*i.e.* the symmetry of the system is already broken). We are currently investigating directed symmetry breaking and asymmetric amplification of ethylenediammonium sulfate in the presence of chiral additives such as amino acids and sugars.²⁶

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Notes and References

‡ It is a common misconception that a racemic mixture is made up of exactly equal amounts of enantiomers.²⁴

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